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	ＡＤＺ		ＡＤＺ
	ＡＥＤ		ＡＥＤ

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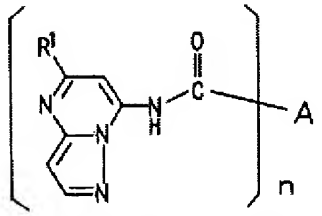
(54)【発明の名称】　カルボキサミド誘導体

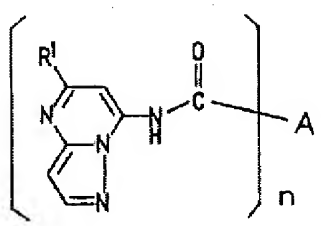
(57)【要約】
【課題】　鎮痛作用、一酸化窒素合成酵素阻害作用等を有する新規化合物を提供する。
【解決手段】　一般式(1)：
【化１】



(1)

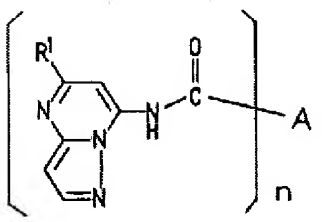
（式中、R^1 は低級アルキル基を示し、ｎは２または３を示し、Ａは、ｎが２のとき、単結合、低級アルキレン基、ベンゼン環またはナフタレン環を示し、ｎが３のとき、ベンゼン環またはナフタレン環を示す。）で表されるカルボキサミド誘導体である。

【特許請求の範囲】
【請求項１】一般式(1)：
【化１】



(1)

（式中、R^1 は低級アルキル基を示し、ｎは２または３を示し、Ａは、ｎが２のとき、単結合、低級アルキレン基、ベンゼン環またはナフタレン環を示し、ｎが３のとき、ベンゼン環またはナフタレン環を示す。）で表されるカルボキサミド誘導体。
【請求項２】Ａは、ｎが２のとき、単結合、低級アルキレン基、ベンゼン環またはナフタレン環であり、ｎが３のとき、ベンゼン環である請求項１記載のカルボキサミド誘導体。
【請求項３】R^1 がｎ－ブチル基である請求項２記載のカルボキサミド誘導体。
【請求項４】ｎが２である請求項３記載のカルボキサミド誘導体。
【請求項５】Ａが低級アルキレン基またはベンゼン環である請求項４記載のカルボキサミド誘導体。
【請求項６】Ｎ，Ｎ’－ビス（５－ｎ－ブチルピラゾロ［１，５－ａ］ピリミジン－７－イル）－１，４－ベンゼンジカルボキサミドまたはＮ，Ｎ’－ビス（５－ｎ－ブチルピラゾロ［１，５－ａ］ピリミジン－７－イル）ヘキサンジアミドである請求項５記載のカルボキサミド誘導体。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、鎮痛作用、一酸化窒素合成酵素阻害作用等を有する新規なカルボキサミド誘導体に関する。
【０００２】
【従来の技術および発明が解決しようとする課題】本発明は鎮痛作用、一酸化窒素合成酵素阻害作用等を有する、文献未記載の新規化合物を提供することを目的とする。
【０００３】
【課題を解決するための手段】本発明は、一般式(1)：
【化２】



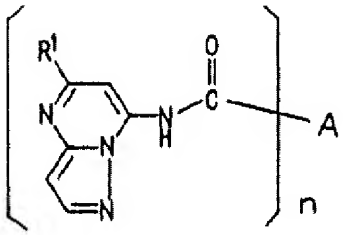
(1)

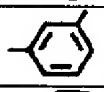
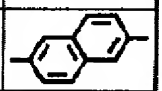
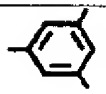
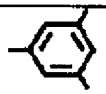
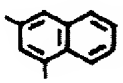
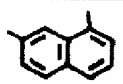
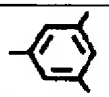
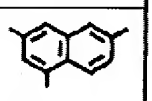
（式中、R^1 は低級アルキル基を示し、ｎは２または３を示し、Ａは、ｎが２のとき、単結合、低級アルキレン基、ベンゼン環またはナフタレン環を示し、ｎが３のとき、ベンゼン環またはナフタレン環を示す。）で表される新規なカルボキサミド誘導体を提供するものである。前記Ａは、ｎが２のとき、単結合、低級アルキレン基、ベンゼン環またはナフタレン環であり、ｎが３のとき、ベンゼン環であるのが好ましい。その際、R^1はｎ－ブチル基であるのがよい。
【０００４】ｎが２のとき、Ａは低級アルキレン基またはベンゼン環であるのがより好ましい。具体例としては、Ｎ，Ｎ’－ビス（５－ｎ－ブチルピラゾロ［１，５－ａ］ピリミジン－７－イル）－１，４－ベンゼンジカルボキサミドおよびＮ，Ｎ’－ビス（５－ｎ－ブチルピラゾロ［１，５－ａ］ピリミジン－７－イル）ヘキサンジアミドが挙げられる。かかる本発明化合物(1) は、鎮痛作用、一酸化窒素合成酵素阻害作用等を有する。従って、本発明化合物(1) は鎮痛剤として、術後疼痛、偏頭痛、痛風、慢性疼痛、神経因請求項疼痛、癌性疼痛等の緩和に有効であり、しかも従来の鎮痛剤にみられるような副作用を示さないという特質がある。
【０００５】また、本発明化合物(1) は、誘導型一酸化窒素合成酵素を選択的に阻害する作用を有しているところから、該酵素の阻害剤として、例えば敗血症、エンドトキシンショック、慢性関節リウマチ等の治療および予防に有効である。
【０００６】
【発明の実施の形態】本発明において、前記低級アルキル基としては、例えばメチル、エチル、プロピル、イソブチル、tert- ブチル、ペンチル、ヘキシル基等の炭素数が１～６の直鎖または分枝鎖状の低級アルキル基が挙げられる。低級アルキレン基としては、例えばメチレン、エチレン、エチリデン、トリメチレン、メチルエチレン、テトラメチレン、ペンタメチレン、ヘキサメチレン基等の炭素数が１～６の直鎖または分枝鎖状の低級アルキレン基が挙げられる。なお、本発明化合物(1) において、ｎが２で、Ａが単結合であるときとは、２つのカルボキサミド残基（－ＨＮＣＯ－）中のカルボニル基が直接結合する場合をいう。
【０００７】本発明のカルボキサミド誘導体(1) の具体例を表１，２に示す。各表において、Ｍｅはメチル基、Ｅｔはエチル基、ｎ－Ｐｒはｎ－プロピル基、ｎ－Ｂｕはｎ－ブチル基、ｎ－Ｐｅはｎ－ペンチル基、ｎ－Ｈｘ

はｎ－ヘキシル基であることを示している。

【０００８】

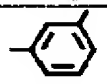
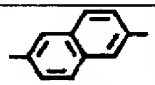
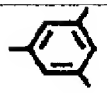
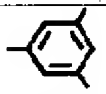
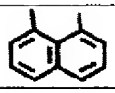
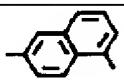
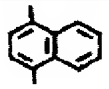
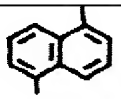
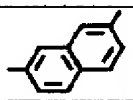
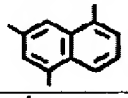
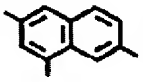
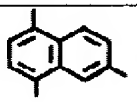
【表１】



R^1	n	A	R^1	n	A
Me	2		Et	2	
Me	2	単結合	Et	2	単結合
Me	2	$-(CH_2)_4-$	Et	2	$-(CH_2)_4-$
Me	2		Et	2	
Me	2		Et	2	
Me	3		Et	3	
n-Hx	2		n-Bu	2	$-CH_2-$
n-Hx	2	単結合	n-Bu	2	CH_3 | $-CH-CH_2-$
n-Hx	2	$-(CH_2)_4-$	n-Bu	2	$-(CH_2)_6-$
n-Hx	2		n-Bu	2	
n-Hx	2		n-Bu	2	
n-Hx	3		n-Bu	3	

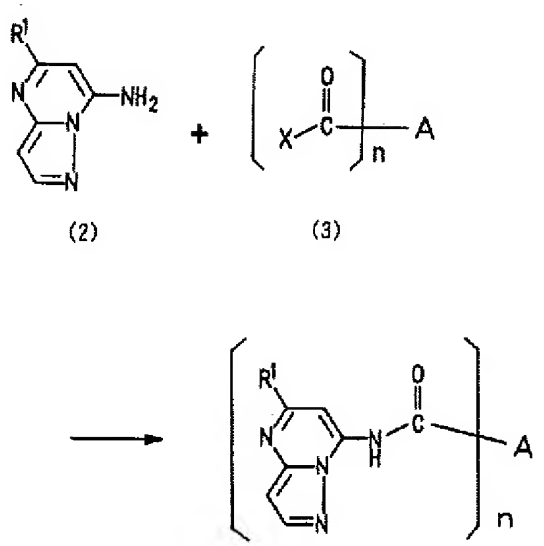
【０００９】

【表２】

R^1	n	A	R^1	n	A
n-Pr	2		n-Pe	2	
n-Pr	2	単結合	n-Pe	2	単結合
n-Pr	2	$-(CH_2)_4-$	n-Pe	2	$-(CH_2)_4-$
n-Pr	2		n-Pe	2	
n-Pr	2		n-Pe	2	
n-Pr	3		n-Pe	3	
n-Bu	2	$-(CH_2)_2-$	n-Bu	2	$\begin{array}{c}CH_3\\ \vert\\ -CH-\end{array}$
n-Bu	2	$-(CH_2)_3-$	n-Bu	2	$-(CH_2)_5-$
n-Bu	2		n-Bu	2	
n-Bu	2		n-Bu	2	
n-Bu	2		n-Bu	3	
n-Bu	3		n-Bu	3	

【００１０】本発明の化合物(1) は、以下のような反応工程式に従って製造することができる。

【化３】



（式中、R^1 、ｎおよびＡは前記と同じであり、Ｘはハロゲン原子を示す。）

【００１１】すなわち、本発明化合物(1) は、化合物(2) を酸ハロゲン化物(3) と反応させて製造することができる。この反応は、適当な溶媒中、脱酸剤の存在下で行うのが好ましい。溶媒としては、例えばベンゼン、トルエン、キシレン、石油エーテル等の芳香族系または脂肪族系炭化水素類；ジエチルエーテル、ジメトキシエタン、テトラヒドロフラン（ＴＨＦ）、１，４－ジオキサン等の鎖状または環状エーテル類；アセトン、エチルメチルケトン、アセトフェノン等のケトン類；ジクロロメタン、クロロホルム、四塩化炭素、１，２－ジクロロエタン等のハロゲン化炭化水素類等が挙げられる。

【００１２】また、前記脱酸剤としては、例えばトリエチルアミン、Ｎ，Ｎ－ジエチルアニリン、Ｎ－メチルモルホリン、ピリジン、４－ジメチルアミノピリジン等の３級アミン類、水酸化ナトリウム、水酸化カリウム等のアルカリ金属水素化物等が挙げられる。上記反応における化合物(2) に対する酸ハロゲン化物(3) および脱酸剤の使用量は、特に限定されないが、通常、化合物(2) に対して、酸ハロゲン化物(3) は１～やや過剰当量程度であるのがよく、脱酸剤は１～過剰当量であるのがよい。反応は室温ないし還流温度の範囲内の温度条件で約０．５～２０時間程度行うのがよい。

【００１３】上記反応によって得られた目的化合物は、通常の分離手段により容易に単離精製することができる。このような分離手段としては、例えば吸着クロマトグラフィー、プレパラティブ薄層クロマトグラフィー、再結晶、溶媒抽出等が挙げられる。本発明化合物(1) は、医薬的に許容される酸付加塩とすることができ、これらの塩も本発明に包含される。上記酸付加塩を形成する酸としては、例えば塩酸、臭化水素酸、硫酸等の無機酸、シュウ酸、フマル酸、マレイン酸、酒石酸、クエン酸、ｐ－トルエンスルホン酸等の有機酸が挙げられる。酸付加塩の形成は、常法に従って行うことができる。

【００１４】また、本発明化合物は、これを常法に従って、例えばナトリウム塩、カリウム塩等のアルカリ金属塩、カルシウム塩、マグネシウム塩等のアルカリ土類金属塩、さらに銅塩等にすることができ、これらの塩も本発明に包含される。本発明化合物(1) は、これを適当な無毒性製剤担体と共に用いて、一般的な医薬製剤の形態として使用される。上記製剤担体としては、製剤の使用形態に応じて通常使用される充填剤、増量剤、結合剤、付湿剤、崩壊剤、表面活性剤、滑沢剤等の希釈剤、賦形剤等が挙げられ、これは得られる製剤の投与単位形態に応じて適宜選択使用される。

【００１５】本発明化合物(1) が使用される医薬製剤の投与単位形態としては、各種の形態が治療目的に応じて選択でき、その代表的なものとしては、錠剤、丸剤、散剤、液剤、懸濁剤、乳剤、顆粒剤、カプセル剤、坐剤、注射剤（液剤、懸濁剤）、軟膏等が挙げられる。

【００１６】錠剤の形態に成形するに際しては、上記製剤担体として例えば乳糖、白糖、塩化ナトリウム、ぶどう糖、尿素、デンプン、炭酸カルシウム、カオリン、結晶セルロース、ケイ酸、リン酸カリウム等の賦形剤；水、エタノール、プロパノール、単シロップ、ぶどう糖液、デンプン液、ゼラチン溶液、カルボキシメチルセルロース、ヒドロキシプロピルセルロース、メチルセルロース、ポリビニルピロリドン等の結合剤；カルボキシメチルセルロースナトリウム、カルボキシメチルセルロースカルシウム、低置換度ヒドロキシプロピルセルロース、乾燥デンプン、アルギン酸ナトリウム、カンテン末、ラミナラン末、炭酸水素ナトリウム、炭酸カルシウム等の崩壊剤；ポリオキシエチレンソルビタン脂肪酸エステル類、ラウリル硫酸ナトリウム、ステアリン酸モノグリセリド等の界面活性剤；白糖、ステアリン、カカオバター、水素添加油等の崩壊抑制剤；第４級アンモニウム塩基、ラウリル硫酸ナトリウム等の吸収促進剤；グリセリン、デンプン等の保湿剤；デンプン、乳糖、カオリン、ベントナイト、コロイド状ケイ酸等の吸着剤；精製タルク、ステアリン酸塩、ホウ酸末、ポリエチレングリコール等の滑沢剤等が使用可能である。

【００１７】さらに錠剤は必要に応じて通常の剤皮を施した錠剤、例えば糖衣錠、ゼラチン被包剤、腸溶被錠、フィルムコーティング錠剤あるいは二重錠、多層錠とすることができる。丸剤の形態に成形するに際しては、製剤担体として例えばぶどう糖、乳糖、デンプン、カカオ脂、硬化植物油、カオリン、タルク等の賦形剤；アラビアゴム末、トラガント末、ゼラチン、エタノール等の結合剤；ラミナラン、カンテン等の崩壊剤等が使用可能である。

【００１８】坐剤の形態に成形するに際しては、製剤担体として例えばポリエチレングリコール、カカオ脂、高級アルコール、高級アルコールのエステル類、ゼラチン、半合成グリセライド等が使用可能である。カプセル剤は常法に従って、通常、本発明化合物(1) を上記で例示した各種の製剤担体と混合して硬質ゼラチンカプセル、軟質カプセル等に充填して調整される。

【００１９】液剤、乳剤、懸濁剤等の注射剤として調製する場合、これらは殺菌されかつ血液と等張であるのが好ましい。注射剤の調製に際しては、希釈剤として例えば水、エチルアルコール、マクロゴール、プロピレングリコール、エトキシ化イソステアリルアルコール、ポリオキシ化イソステアリルアルコール、ポリオキシエチレンソルビタン脂肪酸エステル類等が使用可能である。なお、この場合、等張性の溶液を調製するのに充分な量の食塩、ぶどう糖、グリセリン等を含有させてもよく、また通常の溶解補助剤、緩衝剤、無痛化剤等を添加してもよい。さらに、上記医薬製剤中には、必要に応じて着色剤、保存剤、香料、風味剤、甘味剤等や他の医薬品を含有させることができる。

【００２０】ペースト、クリーム、ゲル等の軟膏剤の形

態に調製するに際しては、希釈剤として例えば白色ワセリン、パラフィン、グリセリン、セルロース誘導体、ポリエチレングリコール、シリコン、ベントナイト等が使用可能である。上記医薬製剤中に含有されるべき本発明化合物(1) の量は、特に制限されず、広範囲より適宜選択されるが、通常、医薬製剤中に約１～７０重量%程度含有させるのがよい。

【００２１】上記医薬製剤の投与方法は特に制限がなく、製剤形態、患者の年齢、性別その他の条件、疾患の程度等に応じて適宜決定される。例えば錠剤、丸剤、液剤、懸濁剤、乳剤、顆粒剤、カプセル剤は経口投与され、注射剤は単独でまたはぶどう糖、アミノ酸等の通常の補液と混合して静脈内投与され、さらに必要に応じて単独で筋肉内、皮内、皮下もくしは腹腔内投与され、坐剤は直腸内投与される。上記医薬製剤の投与量は、その用法、患者の年齢、性別その他の条件、疾患の程度等に応じて適宜決定されるが、通常、本発明化合物(1) の１日当たりの投与量が体重１ｋｇ当たり約０．５～２０ｍｇ、好ましくは１～１０ｍｇ程度とするのがよい。また、上記医薬製剤は１日に１～４回に分けて投与することができる。

【００２２】

【実施例】以下に実施例および試験例をあげて、本発明化合物を詳細に説明する。

実施例１

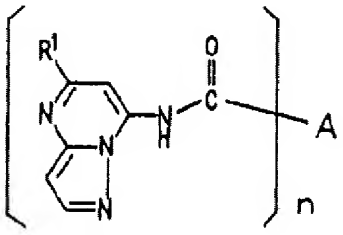
［Ｎ，Ｎ’－ビス（５－ｎ－ブチルピラゾロ［１，５－ａ］ピリミジン－７－イル）－１，４－ベンゼンジカルボキサミドの製造］テレフタル酸０．８３ｇをクロロホルム５ｍＬに溶解し、塩化チオニル１．４３ｇおよびＮ，Ｎ－ジメチルホルムアミド０．２２ｇを加え、室温で１時間、ついで８０℃で４時間撹拌した後、減圧下で濃縮して塩化テレフタロイルを得た。得られた塩化テレフタロイルをジクロロメタン１０ｍＬおよびピリジン１０ｍＬに溶解し、これに氷冷下７－アミノ－５－ｎ－ブチルピラゾロ［１，５－ａ］ピリミジン１．９０ｇを加え、０℃で１時間、ついで室温で１５時間撹拌した。反応液を分液漏斗に移し、希塩酸、水酸化ナトリウム水溶液および水で順次洗浄し、無水硫酸ナトリウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（溶出液：クロロホルム：メタノール＝１０：１）で精製し、さらにクロロホルム－ｎ－ヘキサンより再結晶して、目的化合物の結晶１．３８ｇを得た。この化合物の構造および融点を表３に示す。

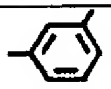
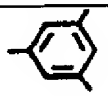
【００２３】実施例２～６

適当な出発原料を用いて、上記実施例１と同様にして、表３に示す構造と融点を有する各化合物を製造した。表３において、ｎ－Ｂｕはｎ－ブチル基を示している。

【００２４】

【表３】



実施例No.	R^1	n	A	融点（℃）／再結晶溶媒
1	ｎ－Ｂｕ	2		２３４～２３６ クロロホルム－ｎ－ヘキサン
2	ｎ－Ｂｕ	2	単結合	２１４～２１６ クロロホルム－ｎ－ヘキサン
3	ｎ－Ｂｕ	2	$-(CH_2)_4-$	１９５～１９７ クロロホルム－ｎ－ヘキサン
4	ｎ－Ｂｕ	2		１４２～１４４ クロロホルム－ｎ－ヘキサン
5	ｎ－Ｂｕ	2		２５８～２６０ クロロホルム－ｎ－ヘキサン
6	ｎ－Ｂｕ	3		２６６～２６８ クロロホルム－ｎ－ヘキサン

【００２５】得られた各化合物のＮＭＲ測定結果を以下に示す。

・実施例１の化合物

^{1}Ｈ－ＮＭＲ（ＣＤＣｌ$_3$）δ：0.99 (6H, t, J=7.4),

1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J=7.9), 6.62 (2H, d, J=2.5), 7.77 (2H, s), 8.06 (2H, d, J=2.5), 8.2-8.3 (4H, m), 10.14 (2H, brs)

・実施例２の化合物

^{1}Ｈ－ＮＭＲ（ＣＤＣｌ$_3$）δ：0.98 (6H, t, J=7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J=7.7), 6.63 (2H, d, J=2.5), 7.63 (2H, s), 8.10 (2H, d, J=2.5), 11.04 (2H, brs)

【００２６】・実施例３の化合物

^{1}Ｈ－ＮＭＲ（ＣＤＣｌ$_3$）δ：0.95 (6H, t, J=7.3), 1.3-1.5 (4H, m), 1.7-1.8 (4H, m), 1.9-2.0 (4H, m), 2.6-2.7 (4H,m), 2.81 (4H, t, J=7.8), 6.55(2H, d, J=2.2), 7.60 (2H, s), 7.99 (2H, d, J=2.2), 9.26 (2H, brs)

・実施例４の化合物

^{1}Ｈ－ＮＭＲ（ＣＤＣｌ$_3$）δ：0.99 (6H, t, J=7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J=7.9), 6.61 (2H, d, J=2.5), 7.79 (2H, s), 7.81 (1H, t, J=7.9), 8.06 (2H, d, J=2.5), 8.29 (2H, d, J=7.9), 8.73 (1H, s), 10.16 (2H, brs)

【００２７】・実施例５の化合物

^{1}Ｈ－ＮＭＲ（ＣＤＣｌ$_3$）δ：0.99 (6H, t, J=7.3), 1.4-1.6 (4H, m), 1.7-1.9 (4H, m), 2.90 (4H, t, J=7.9), 6.62 (2H, d, J=2.5), 7.81 (2H, s), 8.09 (2H, d, J=2.5), 8.1-8.3 (4H, m), 8.61 (2H, s), 10.22 (2H, brs)

・実施例６の化合物

^{1}Ｈ－ＮＭＲ（ＣＤＣｌ$_3$）δ：0.99 (9H, t, J=7.3), 1.4-1.5 (6H, m), 1.7-1.9 (6H, m), 2.89 (6H, t, J=7.8), 6.60 (3H, d, J=2.4), 7.77 (3H, s), 8.04 (3H, d, J=2.4), 8.94 (3H, s), 10.27 (3H, brs)

【００２８】試験例１

［カルボキサミド誘導体(1) の鎮痛活性試験］６週齢Ｓ．Ｄ．系雄性ラットの１群７匹を用い、まず各ラットの左後肢足蹠の疼痛閾値を圧刺激鎮痛効果測定装置（ユニコム社製）を用いて、ランダール・セリット法（Randall.L.O. and Sellitto, J.J., Arch. Int. Pharmcodyn., 111,409 (1957))に準じて測定した。得られた値を「前値」とする。上記前値の測定１時間後に、実験群には供試化合物の５％アラビアゴム懸濁液を、対照群には供試化合物を含まない５％アラビアゴム懸濁液を、それぞれ１０ｍＬ／ｋｇ体重の割合（有効成分投与量：１ｍｇ／ｋｇ体重）となるように経口投与し、さらにその１時間後にサブスタンスＰ（シグマ社製）の生理食塩水溶液（２５ｎｇ／０．１ｍＬ）を、各ラットの左後肢足蹠皮下に注射した。

【００２９】次に、サブスタンスＰ注射の所定時間後に、各群ラットの左後肢足蹠の疼痛閾値を前記と同様にして測定し、これを「後値」とした。各群の後値と前値とから、疼痛閾値回復率（％）を、次式に従って算出した。

【数１】

$$\text{疼痛閾値回復率（\%）} = \frac{\text{（実験群後値）} - \text{（対照群後値）}}{\text{（対照群前値）} - \text{（対照群後値）}} \times 100$$

【００３０】その結果（最大の回復率）を下表に示す。

【表４】

実施例 No.	回復率 (%)	後値測定時 (分後)
1	７２．８	６０
2	２１．５	６０
3	７１．５	６０
4	２７．２	６０
5	２３．４	６０

【００３１】

【発明の効果】本発明のカルボキサミド誘導体は、鎮痛作用および一酸化窒素合成酵素阻害作用を有するという効果がある。

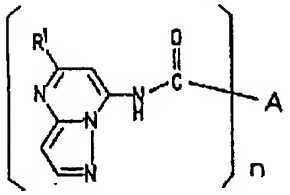
(Abstract)

Object

To put forward a novel compound having analgesic action, nitric oxide synthase inhibitory action or the like.

Method of Solution

It is a carboxamide derivative represented by general formula (1)



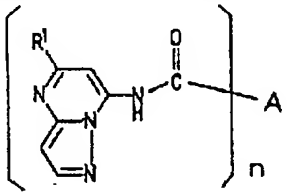
(1)

(wherein, R1 denotes a lower alkyl group, n denotes 2 or 3, and when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring and when n is 3, A denotes a benzene ring or naphthalene ring).

Patent Claims

Claim 1

A carboxamide derivative represented by general formula (1)



(1)

(wherein, R1 denotes a lower alkyl group, n denotes 2 or 3, and when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring and when n is 3, A denotes a benzene ring or naphthalene ring).

Claim 2

A carboxamide derivative in accordance with Claim 1, wherein when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring, and when n is 3, A denotes a benzene ring.

Claim 3

A carboxamide derivative in accordance with Claim 2, wherein R1 is n-butyl group.

Claim 4

A carboxamide derivative in accordance with Claim 3, wherein n is 2.

Claim 5

A carboxamide derivative in accordance with Claim 4, wherein A is lower alkylene group or benzene ring.

Claim 6

A carboxamide derivative in accordance with Claim 5 comprising N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl)-1,4-benzene dicarboxamide or N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl) hexane diamide.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to the following, namely, the novel carboxamide derivative having analgesic action, nitric oxide synthase inhibitory action or the like.

(0002)

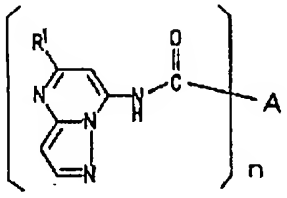
Technology of the Prior Art and Problems to be Overcome by this Invention

This invention has an object of putting forward novel compound containing analgesic action, nitric oxide synthase inhibitory action or the like which had been unmentioned in the literature.

(0003)

Means to Overcome these Problems

This invention puts forward a novel carboxamide derivative represented by general formula (1)



(1)

(wherein, R1 denotes a lower alkyl group, n denotes 2 or 3, and when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring and when n is 3, A denotes a benzene ring or naphthalene ring).

The aforesaid A is preferred to be a single bond, lower alkylene group, benzene ring or naphthalene ring when n is 2, and benzene ring when n is 3. In such case, R1 is preferred to be n-butyl group.

(0004)

More preferably, A is lower alkylene group or benzene ring when n is 2. As embodiment, N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl)-1,4-benzene dicarboxamide and N, N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl) hexane diamide may be proposed. Such compounds of this invention (1) have analgesic action, nitric oxide synthase inhibitory action or the like. Accordingly compounds of this invention (1) are effective for relaxation of postoperative pain, migraine headache, gout, chronic pain, neurogenic claim(sic) pain, cancerous pain or the like as a analgesic, and it has the characteristic that it is almost free from the side effects which are common in prior art analgesics.

(0005)

Moreover, because the compounds of this invention (1) have the action of selectively inhibiting inducible-type nitric oxide synthase, as inhibitor of the said synthase, the said compounds will be effective for prevention and treatment of for example septicemia, endotoxin shock, chronic rheumatism and the like.

(0006)

Conditions for Carrying out this Invention

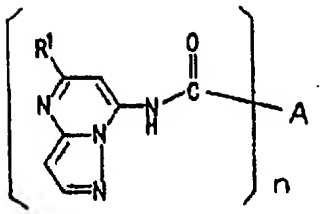
In accordance with this invention, as the aforesaid lower alkyl group, for example straight or branched lower alkyl group of carbon number 1-6 such as methyl, ethyl, propyl, isobutyl, tert-butyl, pentyl, hexyl group and the like may be proposed. As lower alkylene group, for example straight or branched lower alkylene group of carbon number 1-6 such as methylene, ethylene, ethylidene, trimethylene, methylethylene, tetramethylene, pentamethylene, hexamethylene group and the like may be proposed. Moreover, in compounds of this invention (1), the case wherein n is 2 and A is single bond denotes the case wherein the carbonyl groups in two carboxamide residues (-HNCO-) are directly-bonded.

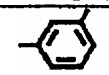
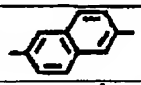
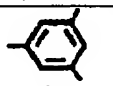
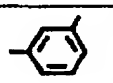
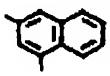
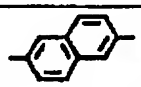
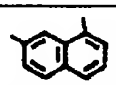
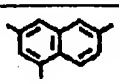
(0007)

Examples of carboxamide derivatives (1) of this invention are shown in Table 1 and 2. In each Table, Me; methyl group, Et; ethyl group, n-Pr; n-propyl group, n-Bu; n-butyl group, n-Pe; n-pentyl group, n-Hx; n-hexyl group is denoted respectivelly.

(0008)

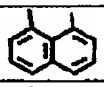
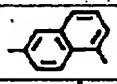
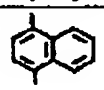
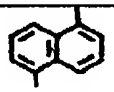
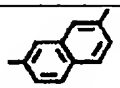
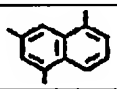
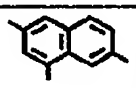
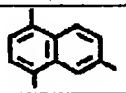
Table 1



R^1	n	A	R^1	n	A
Me	2		Et	2	
Me	2	Single bond	Et	2	Single bond
Me	2	$-(CH_2)_4-$	Et	2	$-(CH_2)_4-$
Me	2		Et	2	
Me	2		Et	2	
Me	3		Et	3	
n-Hx	2		n-Bu	2	$-CH_2-$
n-Hx	2	Single bond	n-Bu	2	CH_3 | $-CH-CH_2-$
n-Hx	2	$-(CH_2)_4-$	n-Bu	2	$-(CH_2)_6-$
n-Hx	2		n-Bu	2	
n-Hx	2		n-Bu	2	
n-Hx	3		n-Bu	3	

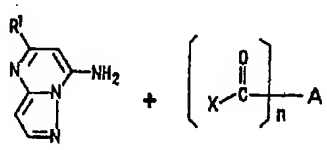
(0009)

Table 2

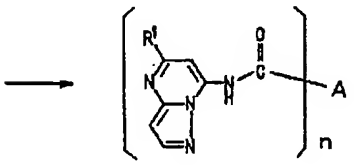
R^1	n	A	R^1	n	A
n-Pr	2		n-Pe	2	
n-Pr	2	Single bond	n-Pe	2	Single bond
n-Pr	2	$-(CH_2)_4-$	n-Pe	2	$-(CH_2)_4-$
n-Pr	2		n-Pe	2	
n-Pr	2		n-Pe	2	
n-Pr	3		n-Pe	3	
n-Bu	2	$-(CH_2)_2-$	n-Bu	2	$-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$
n-Bu	2	$-(CH_2)_3-$	n-Bu	2	$-(CH_2)_5-$
n-Bu	2		n-Bu	2	
n-Bu	2		n-Bu	2	
n-Bu	2		n-Bu	3	
n-Bu	3		n-Bu	3	

(0010)

The compound of this invention (1) can be produced according to the following reaction step equation.



(2) (3)



(wherein, R1, n and A are the same as above, and X denotes a halogen atom).

(0011)

In other words, compounds of this invention (1) can be produced by reacting compound (2) with acid halide (3). This reaction is preferably carried out in the presence of deoxidizer in a suitable solvent. As solvent, aromatic system or aliphatic system hydrocarbons such as benzene, toluene, xylene, light petroleum and the like, chain-form or cyclic ethers such as diethyl ether, dimethoxyethane, tetrahydrofuran (THF), 1,4-dioxane and the like, ketones such as acetone, ethyl methyl ketone, acetophenone and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-chloroethane and the like may be proposed.

(0012)

Moreover, as far as aforesaid deoxidizer is concerned, for example tertiary amine species such as triethylamine, N,N-diethylaniline, N-methylmorpholine, pyridine, 4-dimethylaminopyridine and the like, alkali metal hydride such as sodium hydroxide, potassium hydroxide and the like may be proposed. The quantities of acid halide (3) and deoxidizer used with respect to compound (2) in the aforesaid reaction are not restricted in particular, however usually it is preferably 1 – slightly in excess of equivalent amount of acid halide (3) and 1 - excess equivalent of deoxidizer with respect to compound (2). The reaction is preferably carried out under the temperature condition in a range of room temperature to the reflux temperature for about 0.5-20 hours.

(0013)

The target compound obtained by the aforesaid reaction can be readily isolated and purified by ordinary separation means. As such separation means, for example absorbent chromatography, preparative thin layer chromatography, recrystallization, solvent extraction and the like may be proposed. The compounds of this invention (1) can be made into the pharmacologically acceptable acid addition salt, and such salts are included in this invention, too. As acid forming the aforesaid acid addition salt, inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or the like, organic acid such as oxalic acid, fumaric acid, maleic acid, tartaric acid, citric acid, p-toluenesulfonic acid or the like may be proposed. The formation of acid addition salt can be carried out in accordance with normal methods.

(0014)

Moreover, the compounds of this invention can be also made into alkali metal salt such as sodium salt, potassium salt and the like, alkaline earth metal salt such as calcium salt, magnesium salt and the like and moreover cuprates according to normal method, and these salts are included in this invention, too. The compounds of this invention (1) are used by forming into a general drug preparation by using together with suitable non-toxic preparation carrier. As the aforesaid preparation carrier, excipient, diluent and the like such as filler, expander, binding agent, humectant, disintegrating agent, surface active agent, lubricant and the like, which is conventionally used corresponding to use conditions of preparation may be proposed, and these are suitably selected corresponding to administration unit form of the obtained preparation, and used.

(0015)

As administration unit form of the drug preparation of the compounds of this invention (1), various forms can be selected corresponding to therapy object, and as representative examples thereof, tablet, pill, powder, liquid agent, suspending agent, emulsion, granule, encapsulated formulation, suppository, injection (liquid agent, suspending agent), ointment and the like may be proposed.

(0016)

When forming into tablet, as the aforesaid preparation carrier, for example excipient such as lactose, refined sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silica, potassium phosphate and the like; binding agent such as water, ethanol, propanol, single syrup, glucose liquid, starch liquid, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, methyl cellulose, polyvinylpyrrolidone and the like; disintegrating agent such as carboxymethylcellulose sodium, carboxymethylcellulose calcium, low degree of substitution hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate and the like; surfactant such as polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride and the like; disintegration inhibitor such as refined sugar, stearin, cacao butter, hydrogenated oil or the like; adsorption enhancer such as quaternary ammonium salt group, sodium lauryl sulfate and the like; moisture retaining agent such as glycerol, starch and the like; adsorbent such as starch, lactose, kaolin, bentonite, colloidal silica or the like; lubricant such as purified talc, stearate, boric acid powder, polyethyleneglycol and the like can be used.

(0017)

Further the tablet can be made into the tablet coated with ordinary agent coating in accordance with requirements, for example sugar coated tablet, gelatin encapsulation tablet, enteric coated tablet, film coating tablet or double tablet, multilayer tablet. When formed into the form of a pill, excipient such as for example carrier such as glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and the like; binding agent such as powdered gum arabic, tragacanth powder, gelatin, ethanol and the like; disintegrating agent such as laminaran, agar and the like can be used as preparation carrier.

(0018)

When formed into a form of suppository, as preparation carrier, for example polyethyleneglycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, semi-synthetic glyceride and the like can be used. Encapsulated formulation is usually prepared according to normal method, by mixing compounds of this invention (1) with the various preparation carrier exemplified above and packing into hard gelatin capsule, soft capsule and the like.

(0019)

When prepared as injection agent such as liquid agent, emulsion, suspension and so on, such materials are sterilized and preferably made isotonic with blood. For the preparation of injection, as a diluent, for example, water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species as can be used. Moreover, in this case, sufficient sodium chloride, dextrose or glycerol to form an isotonic solution may be contained in agent of this invention, and moreover ordinary solubilizer, buffer agent, analgesic or the like may be added. Furthermore, in agent of this invention, colorant, preservative, odorant, flavor agent, sweetener and so on and other pharmaceutical can be contained in accordance with requirements.

(0020)

When prepared into a form of ointment such as paste, cream, gel and the like, for example white petrolatum, paraffin, glycerol, cellulose derivative, polyethyleneglycol, silicone, bentonite and the like can be used as diluent. The amount of compounds of this invention (1) to be contained in the agent of this invention is suitably selected from a wide range without restriction in particular, but usually one containing an amount of about 1-70 wt.% approximately in the drug preparation is satisfactory.

(0021)

Administration method of the drug preparation of this invention is not limited in particular, and it is determined corresponding to various formulations, age of patient, the distinction of sex, other conditions, degree of disease or the like. For example, tablet, pill, liquid agent, suspension, emulsion, granule and encapsulated formulation are administered orally, and injection is used alone or mixed with ordinary adjuvant fluid such as dextrose, amino acid or the like, and administered intravenously, and further it is administered alone intramuscularly, intracutaneously, subcutaneously or intraperitoneally in accordance with requirements, and, the suppository is administered rectally. The dose of the aforesaid drug preparation is suitably selected by using the method of use thereof, age of patient, the distinction of sex, other conditions, degree of disease or the like, but usually the amount of the effective ingredient compounds of about 0.5-20 mg, preferably 1-10 mg per 1 kg bodyweight per day is satisfactory, and said preparation can be administered by being divided 1-4 times per day.

(0022)

Examples

Below the compounds of this invention are described in greater detail by reference to Examples and Test Examples.

Example 1

Production of N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl)-1,4-benzene dicarboxamide.

Terephthalic acid 0.83 g was dissolved in chloroform 5 mL, and thionyl chloride 1.43 g and N,N-dimethylformamide 0.22 g were added, and the mixture was stirred at room temperature for one hour, and then at 80°C for four hours, and thereafter it was concentrated under reduced pressure, and terephthaloyl chloride was obtained. The obtained terephthaloyl chloride was dissolved in dichloromethane 10 mL and pyridine 10 mL, and thereto was added 7-amino-5-n-butyl pyrazolo[1,5-a]pyrimidine 1.90 g under ice cooling, and thereafter the mixture was stirred at 0°C for one hour and then at room temperature for 15 hours. The reaction liquor was transferred to separatory funnel, and it was washed successively with dilute hydrochloric acid, sodium hydroxide aqueous solution and water, and after drying with anhydrous sodium sulphate, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; chloroform : methanol = 10 : 1) and it was further recrystallised from chloroform-n-

hexane, and crystalline 1.38 g of the target compound was obtained. The structure and mp. of this compound are shown in Table 3.

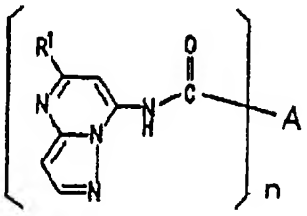
(0023)

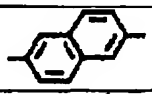
Examples 2-6

Using suitable starting material, each compound having structure and mp. shown in Table 3 was produced in the same way as in aforesaid Example 1. In Table 3, n-Bu denotes n-butyl group.

(0024)

Table 3



Example No.	R^1	n	A	mp. (°C)/recrystallisation solvent
1	n−Bu	2		234～236 chloroform - n-hexane
2	n−Bu	2	Single bond	214～216 chloroform - n-hexane
3	n−Bu	2	$-(CH_2)_4-$	195～197 chloroform - n-hexane
4	n−Bu	2		142～144 chloroform - n-hexane
5	n−Bu	2		258～260 chloroform - n-hexane
6	n−Bu	3		266～268 chloroform - n-hexane

(0025)

The NMR measurement results of the obtained each compound are shown below.

Compound of Example 1

^{1}H-NMR ($CDCl_3$) δ : 0.99 (6H, t, J = 7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J = 7.9), 6.62 (2H, d, J = 2.5), 7.77 (2H, s), 8.06 (2H, d, J = 2.5), 8.2-8.3 (4H, m), 10.14 (2H, brs).

Compound of Example 2

^{1}H-NMR ($CDCl_3$) δ : 0.98 (6H, t, J = 7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J = 7.7), 6.63 (2H, d, J = 2.5), 7.63 (2H, s), 8.10 (2H, d, J = 2.5), 11.04 (2H, brs).

(0026)

Compound of Example 3

^{1}H-NMR ($CDCl_3$) δ : 0.95 (6H, t, J = 7.3), 1.3-1.5 (4H, m), 1.7-1.8 (4H, m), 1.9-2.0 (4H, m), 2.6-2.7 (4H, m), 2.81 (4H, t, J = 7.8), 6.55 (2H, d, J = 2.2), 7.60 (2H, s), 7.99 (2H, d, J = 2.2), 9.26 (2H, brs).

Compound of Example 4

^{1}H-NMR ($CDCl_3$) δ : 0.99 (6H, t, J = 7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J = 7.9), 6.61 (2H, d, J = 2.5), 7.79 (2H, s), 7.81 (1H, t, J = 7.9), 8.06 (2H, d, J = 2.5), 8.29 (2H, d, J = 7.9), 8.73 (1H, s), 10.16 (2H, brs).

(0027)

Compound of Example 5

^{1}H-NMR ($CDCl_3$) δ : 0.99 (6H, t, J = 7.3), 1.4-1.6 (4H, m), 1.7-1.9 (4H, m), 2.90 (4H, t, J = 7.9), 6.62 (2H, d, J = 2.5), 7.81 (2H, s), 8.09 (2H, d, J = 2.5), 8.1-8.3 (4H, m), 8.61 (2H, s), 10.22 (2H, brs).

Compound of Example 6

^{1}H-NMR ($CDCl_3$) δ : 0.99 (9H, t, J = 7.3), 1.4-1.5 (6H, m), 1.7-1.9 (6H, m), 2.89 (6H, t, J = 7.8), 6.60 (3H, d, J = 2.4), 7.77 (3H, s), 8.04 (3H, d, J = 2.4), 8.94 (3H, s), 10.27 (3H, brs).

(0028)

Test Example 1

Analgesic active test of carboxamide derivative (1)

Using 7 animals per group of 6-week old S.D. strain male rat, firstly, pain threshold of left posterior limb footpad of each rat was measured in accordance with Randall • Sellitto method (Randall. L.O. and Sellitto, J.J, Arch, Int, Pharmcodyn, 111, 409 (1957)) using pressure stimulation analgesia effect measuring apparatus (made by Unicom Co.). The obtained value is called "the earlier value". One hour after the measurement of the aforesaid earlier value, 5 % gum arabic suspension of test compound to experimental group and 5 % gum arabic suspension which does not include test compound to control group were respectively administered orally so as to become the proportion of 10 mL/kg

body weight (effective ingredient dose: 1 mg/kg body weight), and after further 1 hour, physiological saline solution of substance P (made by Sigma Corp.) (25 ng 0.1 ml) was injected to the left posterior limb footpad of each rat subcutaneously.

(0029)

Next, pain threshold of the left posterior limb footpad of each group rat was measured after prescribed time of substance P injection in the same way as described above, and it is called "the later value". The pain threshold recovery rate (%) was calculated according to the following equation from the later value and the earlier value of each group.

Equation 1

The pain threshold recovery rate (%) = (the later value of experimental group) - (the later value of control group) / (the earlier value of control group) - (he later value of of control group)

(0030)

The results (the maximum recovery rate) are shown in Table below.

Table 4

Example No.	Recovery rate (%)	The later value measurement time (minutes after)"
1	72.8	60
2	21.5	60
3	71.5	60
4	27.2	60
5	23.4	60

(0031)

Advantages Afforded by this Invention

The carboxamide derivative of this invention has the effect such as having an analgesic action and nitric oxide synthase inhibitory action.

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